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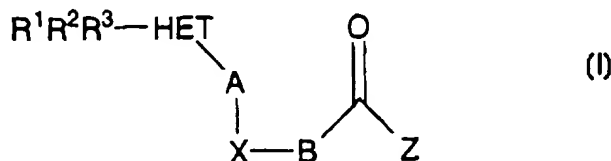
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(54) Title: CARBOXYLIC ACIDS AND ACYLSULFONAMIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(57) Abstract

Compounds of formula (I), as well as pharmaceutically acceptable salts, hydrates and esters thereof, are disclosed. The compounds are useful for treating or preventing prostaglandin mediated diseases. Pharmaceutical compositions containing such compounds and methods of treatment are also included.

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CARBOXYLIC ACIDS AND ACYLSULFONAMIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

BACKGROUND OF THE INVENTION

10 The present invention relates to compounds which are
useful for treating or preventing prostaglandin mediated diseases,
methods of treatment and pharmaceutical compositions containing
such compounds. The compounds are structurally different from
conventional NSAIDs and opiates, and are antagonists of the pain and
15 inflammatory effects of E-type prostaglandins.

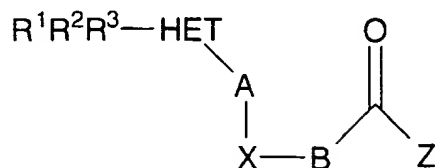
 Two review articles describe the characterization and
therapeutic relevance of the prostanoid receptors as well as the most
commonly used selective agonists and antagonists: *Eicosanoids: From*
Biotechnology to Therapeutic Applications, Folco, Samuelsson, Macclouf,
20 and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and
Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87. An
article from *The British Journal of Pharmacology* (1994, 112, 735-740)
suggests that Prostaglandin E₂ (PGE₂) exerts allodynia through the EP₁
receptor subtype and hyperalgesia through EP₂ and EP₃ receptors in the
25 mouse spinal cord.

 Thus, selective prostaglandin ligands, agonists or antagonists,
depending on which prostaglandin E receptor subtype is being
considered, have anti-inflammatory, antipyretic and analgesic
properties, and in addition inhibit hormone-induced uterine
30 contractions. Moreover, the compounds have anti-cancer effects.

 The compounds have a reduced potential for
gastrointestinal toxicity, a reduced potential for renal side effects, a
reduced effect on bleeding times and a lessened ability to induce asthma
attacks in aspirin-sensitive asthmatic subjects.
35

5 SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula I:



I

10 as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, S(O)_n and N(O)_m wherein m is 0 or 1 and n is 0, 1 or 2;

15 A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)-, -C(R⁷)₂-W-, -W-C(R⁷)₂-, -CR⁷(OR²⁰)-, -C(R⁷)₂-, -C(R⁷)₂-C(OR²⁰)R⁷-, -C(R⁷)₂-C(R⁷)₂- or -CR⁷=CR⁷-, wherein W represents O, S(O)_n or NR¹⁷, with n as previously defined and R¹⁷ as defined below;

20 X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, S(O)_n and N(O)_m, and optionally substituted with R¹⁴ and R¹⁵, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, S(O)_n, NR¹⁷, a bond or -CR¹⁸=CR¹⁸-;

25 B represents - (C(R¹⁸)₂)_p-Y- (C(R¹⁸)₂)_q-

wherein p and q are independently 0-3, such that when Y represents O, S(O)_n, NR¹⁷ or -CR¹⁸=CR¹⁸-, p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or NHSO₂R¹⁹;

30 R¹ R² and R³ independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-HET(R^a)₄₋₉-, (C(R⁴)₂)_pSR⁵-, (C(R⁴)₂)_pOR³-, (C(R⁴)₂)_pN(R⁶)₂-, CN, NO₂-, (C(R⁴)₂)_pC(R⁷)₃-, CO₂R⁹-, CON(R⁶)₂ or (C(R⁴)₂)_pS(O)_nR¹⁰-, wherein n and p are as previously defined;

35 each R⁴ is independently H, F, CF₃ or lower alkyl,

5 or two R^4 groups are taken in conjunction and represent a ring of up to six atoms, optionally containing one heteroatom selected from O, $S(O)_n$ or $N(O)_m$;

each R^5 is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3 , lower alkyl-HET, lower alkenyl-HET or $-(C(R^{16})_2)_pPh(R^{11})_0$ -
 10 2;

each R^6 is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF_3 , Ph, Bn and when two R^6 groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms, optionally containing an additional heteroatom selected from O, $S(O)_n$ or
 15 $N(O)_m$;

each R^7 is independently H, F, CF_3 or lower alkyl, and when two R^7 groups are presents, they may be taken in conjunction and represent an aromatic or aliphatic ring of 3 to 6 members containing from 0-2 heteroatoms selected from O, $S(O)_n$ and $N(O)_m$;

20 each R^8 represents H or R^5 ;

each R^9 is independently H, lower alkyl, lower alkenyl, lower alkynyl, Ph or Bn;

each R^{10} is independently lower alkyl, lower alkenyl, lower alkynyl, CF_3 , $Ph(R^{11})_0$ -3, $CH_2Ph(R^{11})_0$ -3 or $N(R^6)_2$;

25 each R^{11} is independently lower alkyl, SR^{20} , OR^{20} , $N(R^6)_2$, $-CO_2R^{12}$, $-CON(R^6)_2$, $-C(O)R^{12}$, CN, CF_3 , NO_2 or halogen;

each R^{12} is independently H, lower alkyl or benzyl;

each R^{13} is independently H, halo, lower alkyl, O-lower alkenyl, S-lower alkyl, $N(R^6)_2$, CO_2R^{12} , CN, CF_3 or NO_2 ;

30 R^{14} and R^{15} are independently lower alkyl, halogen, CF_3 , OR^{16} , $S(O)_nR^{16}$ or $C(R^{16})_2OR^{17}$;

each R^{16} is independently H, lower alkyl, lower alkenyl, Ph, Bn or CF_3 ;

each R^{17} is independently H, lower alkyl or Bn;

35 each R^{18} is independently H, F or lower alkyl, and when two R^{18} groups are present, they may be taken in conjunction and represent a ring of 3 to 6 members comprising carbon atoms and optionally one heteroatom chosen from O, $S(O)_n$ or N;

- 5 each R^{19} is lower alkyl, lower alkenyl, lower alkynyl, CF_3 ,
HET(R^a)₄₋₉, lower alkyl-HET(R^a)₄₋₉ or lower alkenyl-HET(R^a)₄₋₉;
 each R^{20} is independently H, lower alkyl, lower alkenyl,
lower alkynyl, CF_3 or $Ph(R^{13})_2$
and
10 each R^a is independently selected from the group consisting
of:
H, OH, halo, CN, NO₂, amino, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,
C₁₋₆ alkoxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, C₁₋₆alkylamino,
di-C₁₋₆alkylamino, CF_3 , C(O)C₁₋₆alkyl, C(O)C₂₋₆alkenyl, C(O) C₂₋₆
15 6alkynyl, CO₂H, CO₂C₁₋₆alkyl, CO₂C₂₋₆alkenyl, and CO₂C₂₋₆alkynyl,
said alkyl, alkenyl, alkynyl and the alkyl portions of
alkylamino and dialkylamino being optionally substituted with 1-3 of:
hydroxy, halo, aryl, C₁₋₆ alkoxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, CF_3 ,
C(O)C₁₋₆alkyl, C(O)C₂₋₆alkenyl, C(O)C₂₋₆alkynyl, CO₂H, CO₂C₁₋₆alkyl,
20 CO₂C₂₋₆alkenyl, CO₂C₂₋₆alkynyl, NH₂, NHC₁₋₆alkyl and N(C₁₋₆alkyl)₂.

Pharmaceutical compositions are also included which are
comprised of a compound of formula I in combination with a
pharmaceutically acceptable carrier.

- 25 A method of treating or preventing a prostaglandin
mediated disease is also included which is comprised of administering
to a mammalian patient in need thereof, a compound of formula I in an
amount which is effective for treating or preventing a prostaglandin
mediated disease.

30 DETAILED DESCRIPTION OF THE INVENTION

- The present invention relates to carboxylic acids and
acylsulfonamides, which are ligands at prostaglandin receptors, as well
as a method for treating or preventing a prostaglandin mediated disease
comprising administering to a patient in need of such a treatment of an
35 amount of compound of Formula I which is effective for treating or
preventing a prostaglandin mediated disease.

The invention described in this patent application is
described using the following definitions unless otherwise indicated.

5 HET represents a 5-12 membered aromatic ring system containing 0-3 heteroatoms selected from O, S(O)_n and N wherein n is 0, 1 or 2. HET may be substituted with up to three substituents on the aromatic ring system, R¹, R² and R³. "Aromatic ring systems" as used herein includes aryl and heteroaryl groups such as benzene,
10 naphthalene, biphenyl, pyridine, quinoline, isoquinoline, furan, benzofuran, thiophene, benzothiophene, oxazole, thiazole, imidazole, benzothiazole, triazole, 1,2,5-thiadiazole, thienopyridine, indole, tetrazole, imidazole, benzoxazole, 1,2-methylenedioxybenzene and pyrrole.

15 HET² is a subset of HET and represents a member selected from the group consisting of: phenyl, thienyl, naphthyl, furanyl, thiazolyl, imidazolyl and indolyl.

Aryl refers to aromatic 6-10 membered groups having 1-2 rings and alternating (resonating) double bonds. Examples include
20 phenyl, biphenyl and naphthyl.

Heteroaryl refers to aromatic 5-12 membered groups having alternating (resonating) double bonds and containing from 1-4 heteroatoms selected from O, S(O)_n and N. Examples include the following: : quinoline, furan, benzofuran, thiophene, benzothiophene,
25 thiazole, benzothiazole, 1,2,5-thiadiazole, thienopyridine, oxazole, indole, isoindole, pyridine, isoquinoline, imidazole, thiazole, triazole, 1,3-methylene dioxobenzene, pyrrole and naphthyridine,

Heterocyclyl refers to non-aromatic 5-12 membered cyclic groups having 1-4 heteroatoms selected from O, S(O)_n and N. Examples
30 of heterocyclic groups are piperidine, piperazine, pyrrolidine, tetrahydrofuran, tetrahydropyran and morpholine.

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, S(O)_n and N(O)_m, and optionally substituted with R¹⁴ and R¹⁵, and A and B are
35 attached to the aryl or heteroaryl group X in positions which are ortho relative to each other. Examples are selected from the group consisting of: phenyl, naphthyl, biphenyl, quinoline, furan, benzofuran, pyridyl, pyrrole, thiophene, benzothiophene, thiazole, benzothiazole, 1,2,5-

5 thiadiazole, triazole, 1,2-methylenedioxybenzene, thienopyridine, oxazole and indole.

The terms alkyl, alkenyl, and alkynyl mean linear, branched, and cyclic structures and combinations thereof.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon
10 atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, cyclopropyl, isopropyl, butyl, s- and t-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, heptyl, and the like. When propyl and butyl are recited without the isomeric form being specified, these include all isomers thereof.

15 "Lower alkenyl" means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, cyclopropen-1-yl, cyclohexen-3-yl and the like. When cis or trans is not specified, both are intended in pure form as well as in
20 the form of a mixture of isomers.

"Lower alkynyl" means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl, 2-(cyclopropyl)ethenyl, 3-(cyclobutyl)-1-propynyl and the like.

25 Halogen (halo) includes F, Cl, Br and I.

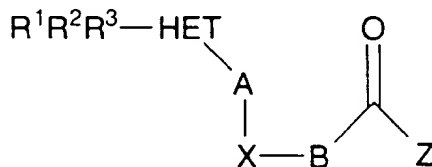
The following abbreviations have the indicated meanings:

	AIBN	=	2,2'-azobisisobutyronitrile
	B.P.	=	benzoyl peroxide
	Bn	=	benzyl
30	CCl ₄	=	carbon tetrachloride
	D	=	-O(CH ₂) ₃ O-
	DAST	=	diethylamine sulfur trifluoride
	DCC	=	dicyclohexyl carbodiimide
	DCI	=	1-(3-dimethylaminopropyl)-3-ethyl
35			carbodiimide
	DEAD	=	diethyl azodicarboxylate
	DIBAL	=	diisobutyl aluminum hydride
	DME	=	ethylene glycol dimethylether
	DMAP	=	4-(dimethylamino)pyridine
40	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethyl sulfoxide
	Et ₃ N	=	triethylamine
	LDA	=	lithium diisopropylamide

5	m-CPBA	=	metachloroperbenzoic acid
	NBS	=	N-bromosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
10	Ph	=	phenyl
	1,2-Ph	=	1,2-benzenediyl
	Pyr	=	pyridinediyl
	Qn	=	7-chloroquinolin-2-yl
	Rs	=	-CH ₂ SCH ₂ CH ₂ Ph
15	r.t.	=	room temperature
	rac.	=	racemic
	THF	=	tetrahydrofuran
	THP	=	tetrahydropyran-2-yl
20	<u>Alkyl group abbreviations</u>		
	Me	=	methyl
	Et	=	ethyl
	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
25	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
	t-Bu	=	tertiary butyl
	c-Pr	=	cyclopropyl
30	c-Bu	=	cyclobutyl
	c-Pen	=	cyclopentyl
	c-Hex	=	cyclohexyl

It is intended that the definition of any substituent (e.g., R⁵,
 35 R⁶, etc.) in a particular molecule be independent of its definition
 elsewhere in the molecule. Thus, -N(R⁶)₂ represents -NHH, -NHCH₃, -
 NHC₆H₅, and the like.

In one aspect of the invention, the invention relates to a
 40 compound represented by formula I:



I

as well as pharmaceutically acceptable salts, hydrates and esters
 thereof, wherein:

5 HET represents a 5-12 membered monocyclic or bicyclic aromatic ring system containing 0-3 heteroatoms selected from O, S(O)_n and N(O)_m wherein m is 0 or 1 and n is 0, 1 or 2;

A is a one or two atom moiety and is selected from the group consisting of: -W-, -C(O)-, -C(R⁷)₂-W-, -W-C(R⁷)₂-, -CR⁷(OR²⁰)-,
 10 -C(R⁷)₂-, -C(R⁷)₂-C(OR²⁰)R⁷-, -C(R⁷)₂-C(R⁷)₂ or CR⁷=CR⁷, wherein W represents O, S(O)_n or NR¹⁷, with n as previously defined and R¹⁷ as defined below;

X represents a 5-10 membered monocyclic or bicyclic aryl or heteroaryl group having 1-3 heteroatoms selected from O, S(O)_n and
 15 N(O)_m, and optionally substituted with R¹⁴ and R¹⁵, and A and B are attached to the aryl or heteroaryl group ortho relative to each other;

Y represents O, S(O)_n, NR¹⁷, a bond or -CR¹⁸ = CR¹⁸-;

B represents - (C(R¹⁸)₂)_p-Y- (C(R¹⁸)₂)_q-

wherein p and q are independently 0-3, such that when Y represents O,
 20 S(O)_n, NR¹⁷ or -CR¹⁸ = CR¹⁸-, p + q = 0-6, and when Y represents a bond, p + q is 1-6;

Z is OH or NHSO₂R¹⁹;

R¹ R² and R³ independently represent H, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkenyl-HET(R^a)_{4.9}, -
 25 (C(R⁴)₂)_pSR⁵, -(C(R⁴)₂)_pOR⁸, -(C(R⁴)₂)_pN(R⁶)₂, CN, NO₂, -(C(R⁴)₂)_pC(R⁷)₃, -CO₂R⁹, -CON(R⁶)₂ or -(C(R⁴)₂)_pS(O)_nR¹⁰, wherein n and p are as previously defined;

each R⁴ is independently H, F, CF₃ or lower alkyl,
 or two R⁴ groups are taken in conjunction and represent a ring of up to
 30 six atoms, optionally containing one heteroatom selected from O, S(O)_n or N(O)_m;

each R⁵ is independently lower alkyl, lower alkenyl, lower alkynyl, CF₃, lower alkyl-HET, lower alkenyl-HET or -(C(R¹⁸)₂)_pPh(R¹¹)₀₋₂;

35 each R⁶ is independently H, lower alkyl, lower alkenyl, lower alkynyl, CF₃, Ph, Bn and when two R⁶ groups are attached to N they may be taken in conjunction and represents a ring of up to 6 atoms,

R ¹ R ² R ³ -Het	A	X	B	Cpd
2-(benzo[b]thiophenyl)	CH ₂	4-F-1,2-Ph	CH=CH	539
5-(1-benzyl)indolyl	CH ₂	4-F-1,2-Ph	CH=CH	540
1-(6-(4-chloro)phenyl) indolyl	CH ₂	4-F-1,2-Ph	CH=CH	541
1-(5-chloro)indolyl	CH ₂	3,2-Pyr	CH=CH	542

5

wherein D = -O(CH₂)₃-O, Qn = 7-chloroquinolin-2-yl, 1,2-Ph = 1,2-benzenediyl, Rs = -CH₂SCH₂CH₂Ph, Pyr = pyridinediyl, c-pr = cyclopropyl and Bn = benzyl.

19. A pharmaceutical composition which is
10 comprised of a compound in accordance with any one of claims 1 to 18 in combination with a pharmaceutically acceptable carrier.

20. A method of treating or preventing a prostaglandin mediated disease which is comprised of administering to a mammalian
15 patient in need of such treatment a compound in accordance with claim 1 in an amount which is effective for treating or preventing a prostaglandin mediated disease.

21. A method in accordance with claim 19 wherein the
20 prostaglandin mediated disease is selected from the group consisting of:
pain, fever or inflammation associated with rheumatic fever, influenza or other viral infections, common cold, low back and neck pain, skeletal pain, post-partum pain, dysmenorrhea, headache, migraine, toothache, sprains and strains, myositis, neuralgia,
25 synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns including radiation and corrosive chemical injuries, sunburns, pain following surgical and dental procedures, immune and autoimmune diseases;
30 cellular neoplastic transformations or metastatic tumor growth;
diabetic retinopathy, tumor angiogenesis;

- 5 prostanoid-induced smooth muscle contraction associated
with dysmenorrhea, premature labor, asthma or eosinophil related
disorders;
- Alzheimer's disease;
 glaucoma;
- 10 bone loss;
 osteoporosis;
 promotion of bone formation;
 Paget's disease;
 cytoprotection in peptic ulcers, gastritis, regional enteritis,
- 15 ulcerative colitis, diverticulitis or other gastrointestinal lesions; GI
bleeding and patients undergoing chemotherapy;
 coagulation disorders selected from hypoprothrombinemia,
haemophilia and other bleeding problems;
- kidney disease;
- 20 thrombosis;
 occlusive vascular disease;
 presurgery;
 and anti-coagulation.
- 25 22. A method in accordance with claim 20 wherein the
prostaglandin mediated disease is selected from the group consisting of:
pain, fever or inflammation.
23. A method in accordance with claim 20 wherein the
- 30 prostaglandin mediated disease is dysmenorrhea.
24. A method in accordance with claim 20, wherein the
compound is co-administered with other agents or ingredients.
- 35 25. A method in accordance with claim 24 wherein the
compound I is co-administered with another agent or ingredient
selected from the group consisting of: an analgesic selected from
acetaminophen, phenacetin, aspirin, a narcotic;

- 5 a COX-2 selective NSAID and a conventional NSAID;
caffeine;
an H₂-antagonist;
aluminum or magnesium hydroxide;
simethicone;
10 a decongestant selected from phenylephrine,
phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine,
naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine;
an antiitussive selected from codeine, hydrocodone,
caramiphen, carbetapentane and dextramethorphan;
15 another prostaglandin ligand selected from misoprostol,
enprostil, rioprostil, ornoprostol and rosaprostol; a diuretic; and
a sedating or non-sedating antihistamine.

26. Use of a compound, salt, hydrate or ester as
defined in any one of claims 1 to 18 in the manufacture of a
20 medicament for treatment or prevention of a prostaglandin
mediated disease.

27. A compound, salt, hydrate or ester as defined in
any one of claims 1 to 18 for use in the treatment or prevention of
a prostaglandin mediated disease.

25 28. A prostaglandin antagonist pharmaceutical
composition comprising an acceptable prostaglandin antagonistic
amount of a compound, salt, hydrate or ester as defined in any one
of claims 1 to 18, in association with a pharmaceutically
acceptable carrier.

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